TETRAHYDROCANNABINOL ANALOGS

BY

SCOTT MACKENZIE, JR.

B.S., University of Pennsylvania, 1942
M.S., University of Illinois, 1944

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE
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Introduction

The active principle of the hemp plant exudate is tetrahydrocannabinol. Many closely related compounds, 1-hydroxy-3-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro - 6 - dibenzopyrans, have been prepared during recent years (1). These synthetic pyrans differ from the natural active principle of marijuana only in the position of the unsaturated bond in the alicyclic portion of the molecule.

The activity of the synthetic homologs depended markedly upon the nature of the alkyl group in the 3- position. Pyrans having normal side-chains from one to eight carbon atoms in length and those having 1-methyl side-chains from five to ten carbon atoms in length have been described (1,2). In both of these series, the characteristic physiological activity of the compounds reached a maximum and then declined sharply. However those pyrans having branched side-chains were far more active than those having straight side-chains. Lengthening of the branched portion of the side-chain decreased the beneficial effect of such branching.

The purpose of the research reported in this thesis was to synthesize a tetrahydrocannabinol having a 1,1-dimethylalkyl side-chain in the 3- position.

Dicussion

1-Hydroxy-3-(1,1-dimethylbutyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran was synthesized from 3,5-dimethoxybenzoic acid through the following intermediate compounds:

Ethyl 3,5-Dimethoxybenzoate
3,5-Dimethoxybenzhydrazide
3,5-Dimethoxybenzoyl-*p*-toluenesulfonylhydrazine
3,5-Dimethoxybenzaldehyde

3,5-Dimethoxybenzyl Alcohol
3,5-Dimethoxybenzyl Chloride
3,5-Dimethoxybenzyl Cyanide
2-Methyl-2-(3,5-dimethoxyphenyl)propionitrile
2-Methyl-2-(3,5-dimethoxyphenyl)-3-pentanone
2-Methyl-2-(3,5-dimethoxyphenyl)-3-pentanol
2-Methyl-2-(3,5-dimethoxyphenyl)-3-pentene
2-Methyl-2-(3,5-dimethoxyphenyl)pentane
2-Methyl-2-(3,5-dihydroxyphenyl)pentane
1-Hydroxy-3-(1,1-dimethylbutyl) - 9 - methyl - 7,8,9,10-tetrahydro-6-dibenzopyrone.

A similar synthesis, designed to produce a pyran with a 1,1-dimethylheptyl side-chain, was completed as far as the olefin stage; 2-methyl-2-(3,5-dimethoxyphenyl)-3-octene was prepared.

Prepared in the usual manner from 3,5-dimethoxybenzamide were two additional pyrans. The two side-chains in the 3- position were, respectively, 1,2-dimethylbutyl and 1-ethyl-2-methylpropyl.

Synthesis of a pyran with a 1,2-dimethylheptyl side-chain was partially completed; 3-methyl-2-(3,5-dimethoxyphenyl)-2-octene was prepared.

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2. Adams, Aycock and Loewe, private communication.

VITA

The author was born in Sedalia, Missouri, on March 10, 1920. He attended the public schools of Modesto, California.

He enrolled in the Towne Scientific School of the University of Pennsylvania in October, 1938, and graduated in June, 1942, with a degree of Bachelor of Science.

From October, 1942, to June, 1944, he was enrolled in the Graduate School of the University of Illinois and held teaching assistantships during this period. He received the degree of Master of Science in 1944.

From June, 1944, until March, 1946, he was employed as a research chemist by E. I. du Pont de Nemours, Inc., at Waynesboro, Virginia. Since the latter date, he has been enrolled in the Graduate School of the University of Illinois and has held an Eastman Kodak Fellowship.

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